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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	**PAPER NUMBER**
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/774,176	CARROLL ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/20/07, 2/22/07, 3/14/07 & 3/20/07*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37,39,41,42,48-51 and 53* is/are pending in the application.

4a) Of the above claim(s) *42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37,39,41,42,48-51 and 53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/14/07 & 2/20/07 & 5/13/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants are required under 37 C.F.R. 1.821(d) to amend the specification to list the appropriate SEQ ID NOS for sequences disclosed in the specification (for example, page 56 at lines 6 and 7).

2. Applicant's amendment filed 2/20/07 and Applicant's responses filed 3/20/07, 2/22/07 and 3/14/07 are acknowledged and have been entered.

3. Applicant is reminded of Applicant's election with traverse of Group I (newly added claims 43-53), and species of SEQ ID NO: 5 in responses filed 3/22/06 and 6/5/06 and in Applicant's amendment and response filed 9/15/06.

Claims 37, 39, 41, 48-51 and 53 are presently being examined.

4. The disclosure is objected to because of the following informalities:

a. There are two sets of page numbers on each page of the specification and originally filed claims, *i.e.*, one at the top center and one at the bottom left.

b. There is no heading for the Brief Description of the Drawings.

c. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, for example on page 6 at lines 5-6, on page 28 at lines 5 and 11-12, on page 27 at line 25, on page 28 at lines 5 and 11, on page 30 at line 10, on page 31 at lines 2, 5 and 8. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

d. The use of the trademarks LIPOFECTIN, EUDRAGIT, AMPHIGEN AND ALHYDROGEL have been noted in this application on page 49 at line 23, page 42 at line 2, and page 41 at lines 4-5. They should be capitalized wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate correction(s) is/are required.

The Examiner notes Applicant's argument (in the amendment filed 2/20/07 on pages 6-7) that these objections be held in abeyance. However, the objections may not be held in abeyance.

5. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The Examiner notes Applicant's argument (in the amendment filed 2/20/07 on page 7) that this objection be held in abeyance. However, the objection may not be held in abeyance.

The following are new grounds of rejection necessitated by Applicant's amendment filed 2/20/07.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 37, 39, 41, 48-51 and 53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the. . .claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicant had possession at the time of invention of the expression vector(s) recited in the instant claims.

The instant claims encompass an expression vector or a pair of vectors, including poxvirus vector(s) such as MVA, wherein the said vector(s) *comprise* a nucleotide sequence encoding (*i.e., comprising*) a human 5T4 antigen that is *modified* to differ from any naturally occurring 5T4 antigen and comprises a peptide epitope of 5T4 antigen, including one of SEQ ID NO: 5-17, and wherein the modification is any modification of any portion of any 5T4 antigen, and wherein in the instance of SEQ ID NO: 5-17, undisclosed flanking amino acid sequences are present that are not in the 5T4 protein of origin from which the SEQ ID NO is a subsequence or an altered subsequence, and including for claims 37 and 39-41 wherein the modified 5T4 antigen is capable of inducing an anti-tumor immunotherapeutic response in a subject, including wherein the said response is a CTL or an antibody response, and including for claims 48-51 and 53 wherein the vectors are for priming and boosting an immune response in a subject. As such, the claims are drawn to an expression vector comprising a nucleotide sequence encoding a peptide of partially disclosed structure.

As the complete structures of the claimed peptides are not disclosed, among the distinguishing relevant identifying characteristics considered in this analysis are partial structure, physical and/or chemical properties, functional characteristics, known or disclosed correlation between structure and function, and method of making.

The specification discloses that human 5T4 is characterized by Myers *et al*, the sequence of which appears in GenBank at accession no. Z20983 and is set out as SEQ ID NO: 1 of the instant application (page 5 at lines 13-15). Evidentiary reference GenEmbl Accession No. Z209083 teaches the sequence of Accession no. Z29083, human 5T4 gene for 5T4 oncofetal antigen. It is noted by the Examiner that the elected species SEQ ID NO: 5 is a subsquence of the human 5T4 protein, and as such it is not modified. Therefore instant claim 41 encompasses an expression vector wherein the modified 5T4 antigen comprises a peptide sequence selected from SEQ ID NO: 5 or any of the other recited SEQ ID NO that are unaltered subsequences of human 5T4 protein flanked by undisclosed sequence that are not contiguous flanking sequence from human 5T4 protein.

The specification discloses that a modified 5T4 antigen is a polypeptide that has been truncated, extended or otherwise mutated such that it differs from naturally occurring 5T4. The specification discloses that 5T4 peptides may be mutated by amino acid insertion, deletion or substitution, may be any length, but are advantageously between 5-25 amino acid residues, and preferably between 6 and 15 amino acid residues. The specification discloses that the peptides are able to bind HLA molecules and to induce CTL responses against wild-type 5T4 in subjects, often more effectively than full length 5T4 (page 5 at lines 22-32). The specification further discloses that human 5T4 consists of SEQ ID NO: 1, mouse 5T4 consists of SEQ ID NO: 2 and canine 5T4 consists of SEQ ID NO: 3, and that the invention comprises species and allelic variations of 5T4, as well as fragments, preferably distinct epitopes, and variants thereof comprising amino acid insertions, deletions or substitutions that retain the antigenicity of 5T4 (page 5 at lines 12-20).

As to the issue of "human 5T4 antigen...modified to differ from a naturally occurring 5T4 antigen," the specification discloses only three naturally occurring 5T4 antigens as enunciated supra, *i.e.,* that of SEQ ID NO: 1-3, or human, mouse and canine.

The specification discloses that MVA vectors comprising nucleic acid molecules that correspond to the coding sequence of human or mouse 5T4 were effective in raising a high titre of antibodies when administered to mice (Example 9), and that in mouse tumor models, mice vaccinated with MVA-h5T4 or MVA-m5T4 were able to mount anti-tumor activity when challenged with a syngeneic tumor line expressing the human or mouse 5T4 protein with resulting tumor retardation or lowered tumor burden (Examples 3-8).

As to the issue of "*comprise and encodes*", the specification does not disclose wherein the vector(s) encode a nucleic acid sequence comprising one of SEQ ID NO: 5-17 with undisclosed flanking sequences, nor variants of altered subsequences of 5T4 proteins comprising undisclosed flanking sequences not in the protein of origin, nor species other than human, murine or canine.

The art recognizes that for a peptide to be a T cell epitope, the length of the peptide is important for binding to HLA (along with the presence of anchor (or "motif") amino acid residues present within the peptide). The peptides that bind to class I molecules have a predominant length, *i.e.,* a minimum of 8 or 9 amino acid residues for a class I MHC restricted T cell epitope peptide. A primary factor for this is that amino acid residues at the amino- and carboxy-termini of peptides binding to class I molecules interact with conserved amino acid residues in pockets ("A","F") located at opposite ends of the binding groove of the class I molecule, giving rise to a common orientation of the peptides in the binding site (Engelhard at page 14, column 1, lines 16-27, of record) Thus, the amino acid residues at the peptides' termini make a network of hydrogen bonds with conserved residues on the sides and bottom of the peptide binding groove of class I molecules. These interactions are important for holding the peptides in the binding groove and for stabilizing the complex (Guo *et al* at page 366, column 1 lines 1-10, of record) "...the preferred length (of the peptide) is determined by the minimum amount of peptide required to span the center of the binding site and optimize the interactions at the ends", but that the predominant length is 9 amino acid residues (Engelhard at page 14, column 1, lines 23-27, of record). The minimum length for a peptide to be a T cell epitope for class II MHC is about 12 amino acid residues (Rammensee *et al* at page 181, column 2, first full paragraph, of record).

In addition, the art recognizes that flanking sequences influence the processing and presentation of CTL epitopes (Eisenlohr *et al*, Shastri *et al*, Bergmann *et al*, Wang *et al*, Perkins *et al*, Theoboald *et al* and Gileadi *et al*, all of record) and that immunodominance can be affected by the context of the epitope within the protein molecule and that junctional neoepitopes can be created (Perkins *et al,* of record) or that immunodominant epitopes can be completely silenced by contiguous sequences (Wang *et al,* of record).

The specification provides no disclosure that modified 5T4 antigens encoded in the vector(s) of the claimed invention are immunogenic, either as CTL, Th or B cell epitopes. *In vivo* studies disclosed in the instant specification utilize whole unaltered human or murine 5T4 as enunciated supra.

Celis *et al* (of record) teach that in order to establish whether a peptide is immunogenic said peptide needs to be tested in assays that actually establish that a peptide is immunogenic. Further, although *experimental* ranking schemes are available for predicting relative binding strengths of some HLA binding nonapeptides, and assays are available to test the binding of peptides to HLA, an undue amount of experimentation would be involved in determining peptides from the many possibilities that would be capable of binding to HLA, inducing a CTL response and producing a clinical endpoint. Celis *et al* teach "In addition to MHC binding, other factors such as antigen processing, peptide transport and the composition of the T-cell receptor repertoire could determine whether peptides can function as effective CTL antigens." Ochoa-Garay *et al* (of record) teach that "In summary, the results in this report indicate that the immunogenicity of a peptide cannot always be predicted from its affinity for class I or the presence of class I binding motifs. In addition, our data show that variables such as CTL precursor frequency, peptide hydrophobicity and stability can influence the *in vitro* induction of CTL responses" (especially page 279, last sentence and continuing onto page 280). Karin *et al* (of record) teach that amino acids in an MHC binding peptide that are not the amino acids which participate in MHC binding can have a profound effect on whether or not a peptide is immunogenic. Chaux *et al* (Int. J. Cancer 77 538-542, 1998, of record) teach that it is unclear if peptides from tumor specific proteins possessing anchor residues for binding to class I MHC produce CTL responses in patients vaccinated with the said peptides.

There is no description in the instant specification of which of the trillions of modified 5T4 antigens encompassed by the claimed invention would be immunogenic.

In addition, the specification provides no disclosure that the SEQ ID NO recited in instant claim 41 that were selected by prediction algorithm and shown to bind to HLA-A*0201 are immunogenic, *i.e.,* induce CTL, and can produce a clinical endpoint in inducing an anti-tumor immunotherapeutic response. Although the instant specification discloses that immunization with vector(s) encoding unmodified full-length human or murine 5T4 protein in mouse tumor models could produce a clinical response *in vivo*, there is no disclosure that the isolated SEQ ID NO can produce the clinical result, even if capable of inducing CTL.

Evidentiary reference Berger *et al* (Int. J. Cancer. 111: 229-237, 2004) teach "Since strong CTL responses as observed in this patient are the goal of cancer vaccination but are so far only rarely observed, the thorough analysis of patients exhibiting either exceptional clinical and/or immunologic response appears critical to understanding how vaccine therapies work and can be further improved." (abstract). Berger *et al* further teach "immune therapy for tumor patients aims at harnessing the immune system to fight cancer. Indeed, clinical trials have already shown that tumor-specific T cells can be induced even in advanced cancer patients. The induction of tumor-specific T cells, however, is not necessarily associated with a clinical response. A major obstacle in evaluating the success of a cell-based immunotherapy lies in the fact that systemic

immune responses detected in the blood may not reflect the actual situation in the tumor." (column 1, page 229). Berger *et al* teach "...tumor-reactive T-cell clones persisted for prolonged time in circulation but failed to infiltrate the analyzed tumor lesions. A possible explanation for this discrepancy is provided by the recent report from a transgenic mouse model that tumors may develop an intrinsic resistance to leukocyte infiltration and effector function that prevents even persistently high levels of activated tumor-specific T lymphocytes from eradicating the tumor" (paragraph spanning columns 1-2 on page 236).

Evidentiary reference Celis (J. Clin. Invest. 2002, 110 (12: 1765-1768) teaches that "Unfortunately, the advantages that peptide vaccines have to offer are to some extent diminished by their inherent lack of immunogenicity, which so far has been reflected by their not-so-spectacular results in the clinic. Because the immune system in most species has evolved through time to fight life threatening infectious agents (and perhaps tumors), it should not be surprising that vaccines consisting of aseptic, endotoxin-free peptides are likely to be ignored and will likely be ineffective at inducing T cell immunity. In addition, peptides that are injected in aqueous solutions will be unsuccessful at stimulating CTL responses, either because of their rapid biodegradation (e.g., by proteases) or, worse, because of the induction of T cell tolerance/anergy, which results from the antigenic stimulation of CTLs by non-professional APCs." Celis further teaches that an additional complication resulting from the use of synthetic peptide-derived vaccines is the induction of low affinity CTLs, that while capable of killing target cells that are exogenously pulsed with peptide, are not able to recognize the target cells that naturally process and present the peptide epitope, such as malignant cells. These low quality CTLs would have little effect in fighting and controlling disease (especially page 1765 through the paragraph spanning pages 1765-1766.

Evidentiary reference Marchand *et al* (Int. J. Cancer 80: 219-230, 1999) teach "Considerable further progress is needed... before immunization with tumor-specific antigens recognized by T cells becomes an effective and generally applicable cancer therapy." (second to last sentence of article).

Evidentiary reference Marchand *et al* (Exp. Opin. Biol. Ther. 1(3): 497-510, 2001) teach "It is fair to say that in patients vaccinated with defined antigen, the immune responses induced have been so far very poor, if present. In some studies, immune responses were reported for some patients but without any correlation with the clinical responses. In addition, some patients with complete and long-term regressions of several melanoma metastases failed to mount a detectable response against the antigen present in the vaccine." (last paragraph at column 2 on page 505).

Evidentiary reference Bodey *et al* (Anticancer Research 20: 2665-2676, 2000) teach "while cancer vaccine trials have yielded tantalizing results, active immunotherapy has not yet become an established modality of anticancer therapy (page 2665 at column 2). Bodey *et al* further teach "the use of active specific immunotherapy for cancer is still in its infancy despite several decades of clinical and basic research" (page 2668 at column 2).

Evidentiary reference Gao *et al* (J. Immunother. 23: 643-653, 2000) found that although anti-tumor CTL response was enhanced by immunization, the tumors failed to regress due to an association with lack of CTL migration to the tumor sites (abstract). Thus, Gao *et al* teach that activation of peptide epitope-specific CTL is not an appropriate endopoint, and an estimation of efficacy based upon this factor is not predictive of actual efficacy of treatment *in vivo*.

Evidentiary reference Morel *et al* (Immunity 12: 107-117, 2000) teach the treatment of target cells for at least one week with IFN-γ to induce immunoproteasome expression in said target cells, and further teach that a number of antigenic peptides that are efficiently produced by the standard proteasome are not produced by the immunoproteasome. Morel *et al* further teach that a major difference between the two forms of proteasomes in terms of catalytic activity is the severely reduced ability of the immunoproteasome to cleave after acidic residues and also after residues with branched side chains, such as valine (paragraph spanning pages 113-114). Morel *et al* teach that an IFN-γ rich environment such as that found in a lymph node or a tumor mass heavily infiltrated with T cells could cause a proteasome switch in the tumor cells resulting in a lack of presentation of certain tumor antigens and escape from CTL attack (especially first sentence of the third full paragraph at column 1 on page 114).

Evidentiary reference Boon *et al* (Ann. Rev. Immunol. 2006, 24: 175-208) teach "Therapeutic vaccination of metastatic melanoma patients with these antigens [*i.e.,* melanoma antigens] is followed by tumor regressions in only a small minority of the patients (page 175, abstract). Boon *et al* further teach "In conclusion, therapeutic success following vaccination may not depend on the number of T cells produced directly by the vaccine, but rather on the production of a T cell clone with functional properties that enable it to migrate to the tumor and resist the local immunosuppressive environment long enough to initiate a regression process...To achieve therapeutic success, investigators will probably need to understand the cause of the local immunosuppression in the tumors and find counteracting agents. As stated above, the list of possible immunosuppressive agents present in tumors is considerable. But it will be important to find whether, for each type of tumor, there is a prevalent immunosuppressive agent. Just as many types of tumors have preferred oncogenic pathways that differ from one type of tumor to another, each type of tumor may also have preferred immunosuppressive processes that we must identify to achieve therapeutic success...Therapeutic vaccination of cancer has not yet proved to be effective enough to become a generally applied cancer treatment...We do not believe

that melanoma patients suffer from a degree of general immunosuppression, which we believe is restricted to very late-stage patients who are not included in most studies...Therefore, the difference in the quality of the response would be due to a chance event determining, for instance, the functional properties of the unique or the few responder T cell clones elicited by the vaccine. In that case, it will be essential to understand what this crucial functional property is. At the other extreme, the antivaccine T cell responses would be similar in all patients, but the level of resistance of the tumors would vary considerably. In that case investigators would need to identify the main component of this resistance and find ways to counteract it." (especially pages 193-194).

In view of the aforementioned problems regarding description of the claimed invention, the specification does not provide an adequate written description of the invention claimed herein. See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398, 1404-7 (Fed. Cir. 1997). In University of California v. Eli Lilly and Co., 39 U.S.P.Q.2d 1225 (Fed. Cir. 1995) the inventors claimed a genus of DNA species encoding insulin in different vertebrates or mammals, but had only described a single species of cDNA which encoded rat insulin. The court held that only the nucleic acids species described in the specification (*i.e.,* nucleic acids encoding rat insulin) met the description requirement and that the inventors were not entitled to a claim encompassing a genus of nucleic acids encoding insulin from other vertebrates, mammals or humans, id. at 1240. The Federal Circuit has held that if an inventor is "unable to envision the detailed constitution of a gene so as to distinguish it from other materials. . .conception has not been achieved until reduction to practice has occurred", Amgen, Inc. v. Chugai Pharmaceutical Co, Ltd., 18 U.S.P.Q.2d 016 (Fed. Cir. 1991). Attention is also directed to the decision of The Regents of the University of California v. Eli Lilly and Company (CAFC, July 1997) wherein is stated: "The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 222 USPQ 369, 372-373 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, as we have previously held, a cDNA is not defined or described by the mere name "cDNA," even if accompanied by the name of the protein that it encodes, but requires a kind of specificity usually achieved by means of the recitation of the sequence of nucleotides that make up the cDNA." See Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606.

The instant disclosure does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera, including an expression vector(s) comprising a nucleic acid sequence encoding a modified 5T4 antigen, said antigen that includes a polypeptide that has been truncated, extended or otherwise mutated, by amino acid insertion, deletion or substitution, such that it differs from any

naturally occurring 5T4, variant or allele derived from any species. Since the disclosure fails to provide sufficient relevant identifying characteristics, and because the genus is highly variant, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus as broadly claimed.

Applicant's arguments in the amendment filed 2/20/07 have been fully considered, but are not persuasive.

Applicant's arguments are of record on pages 7-9 of the said amendment, briefly: (1) allegedly no prima facie case of inadequate written description has been presented, (2) there is clear guidance for a "strong presumption that an adequate written description of the claimed invention is present when the application is filed", (3) the claims are directed to a modified human 5T4 antigen where the full sequence of the antigen is disclosed and where methods to modify a known antigen sequence are known and readily available, and where methods to produce and characterize modified antigens as containing an HLA CTL peptide epitope and/or capable of inducing an antitumor immunotherapeutic response in a subject are also known and readily available, (4) representative species of human 5T4 sequences such as those featured in claim 41 may be encoded by the genus of vectors as claimed, (5) no reduction to practice is required.

It is the Examiner's position that: (1) a prima facie case of inadequate written description is set forth supra, (2) clear guidance does not exist as enunciated in the instant rejection supra, (3) although the sequence of human 5T4 is known, the claims are drawn to a vector comprising a nucleotide sequence that encodes a modified human 5T4 antigen that differs from any naturally occurring 5T4 antigen, the evidentiary references indicate that many factors influence immunogenicity of peptide sequences including the context they are presented in in terms of flanking sequences, and that even when CTL epitopes are immunogenic, there is not a structure function correlation in the ability to induce an antitumor immunotherapeutic response in a subject, (4) the species of peptides recited in instant claim 41 are predicted to bind to HLA-A*0201, but may not be immunogenic or capable of inducing an antitumor immunotherapeutic response in a subject, (5) the production of antibodies in mice injected with MVA vectors comprising nucleic acid molecules that correspond to the coding sequence of the entire human or mouse 5T4 proteins able to mount anti-tumor activity when challenged with a syngeneic tumor line expressing the human or mouse 5T4 protein is not representative of immunization with a subsequence of a human or mouse 5T4 encoding nucleic acid molecule wherein the subsequence contains a CTL epitope along with undisclosed flanking sequences and wherein the cancer is established.

8. Claims 37, 39, 41, 48-51 and 53 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification has not enabled the breadth of the claimed invention because the claims encompass an expression vector or a pair of vectors, including poxvirus vector(s) such as MVA, wherein the said vector(s) *comprise* a nucleotide sequence encoding (*i.e., comprising*) a human 5T4 antigen that is modified to differ from a naturally occurring 5T4 antigen and comprises a peptide epitope of 5T4 antigen, including one of SEQ ID NO: 5-17, including wherein the modified 5T4 antigen is capable of inducing an anti-tumor immunotherapeutic response in a subject, including wherein the said response is a CTL or antibody response, an including wherein the vectors are for priming and boosting an immune response in a subject. The state of the art is such that it is unpredictable in the absence of appropriate evidence whether the claimed expression vector(s) can be made and/or used.

The specification discloses that human 5T4 is characterized by Myers *et al*, the sequence of which appears in GenBank at accession no. Z20983 and is set out as SEQ ID NO: 1 of the instant application (page 5 at lines 13-15). Evidentiary reference GenEmbl Accession No. Z209083 teaches the sequence of Accession no. Z29083, human 5T4 gene for 5T4 oncofetal antigen. It is noted by the Examiner that the elected species SEQ ID NO: 5 is a subsquence of the human 5T4 protein, and as such it is not modified. Therefore instant claim 41 encompasses an expression vector wherein the modified 5T4 antigen comprises a peptide sequence selected from SEQ ID NO: 5 or any of the other recited SEQ ID NO that are unaltered subsequences of human 5T4 protein flanked by undisclosed sequence that are not contiguous flanking sequence from human 5T4 protein.

The specification discloses that a modified 5T4 antigen is a polypeptide that has been truncated, extended or otherwise mutated such that it differs from naturally occurring 5T4. The specification discloses that 5T4 peptides may be mutated by amino acid insertion, deletion or substitution, may be any length, but are advantageously between 5-25 amino acid residues, and preferably between 6 and 15 amino acid residues. The specification discloses that the peptides are able to bind HLA molecules and to induce CTL responses against wild-type 5T4 in subjects, often more effectively than full length 5T4 (page 5 at lines 22-32). The specification further discloses that human 5T4 consists of SEQ ID NO: 1, mouse 5T4 consists of SEQ ID NO: 2 and canine 5T4 consists of SEQ ID NO: 3, and that the invention comprises species and allelic variations of 5T4, as well as fragments, preferably distinct epitopes, and variants thereof comprising amino acid insertions, deletions or substitutions that retain the antigenicity of 5T4 (page 5 at lines 12-20).

As to the issue of "human 5T4 antigen...modified to differ from a naturally occurring 5T4 antigen," the specification discloses only three naturally occurring 5T4 antigens as enunciated supra, *i.e.,* that of SEQ ID NO: 1-3, or human, mouse and canine. It would require undue experimentation to determine which modified human 5T4 sequences differ from undisclosed naturally occurring 5T4 antigens.

The specification discloses that MVA vectors comprising nucleic acid molecules that correspond to the coding sequence of human or mouse 5T4 were effective in raising a high titre of antibodies when administered to mice (Example 9), and that in mouse tumor models, mice vaccinated with MVA-h5T4 or MVA-m5T4 were able to mount anti-tumor activity when challenged with a syngeneic tumor line expressing the human or mouse 5T4 protein with resulting tumor retardation or lowered tumor burden (Examples 3-8).

As to the issue of "*comprise and encodes*", the specification does not disclose wherein the vector(s) encode a nucleic acid sequence comprising one of SEQ ID NO: 5-17 with undisclosed flanking sequences, nor variants of altered subsequences of 5T4 proteins comprising undisclosed flanking sequences not in the protein of origin, nor species other than human, murine or canine.

The art recognizes that for a peptide to be a T cell epitope, the length of the peptide is important for binding to HLA (along with the presence of anchor (or "motif") amino acid residues present within the peptide). The peptides that bind to class I molecules have a predominant length, *i.e.,* a minimum of 8 or 9 amino acid residues for a class I MHC restricted T cell epitope peptide. A primary factor for this is that amino acid residues at the amino- and carboxy-termini of peptides binding to class I molecules interact with conserved amino acid residues in pockets ("A","F") located at opposite ends of the binding groove of the class I molecule, giving rise to a common orientation of the peptides in the binding site (Engelhard at page 14, column 1, lines 16-27.) Thus, the amino acid residues at the peptides' termini make a network of hydrogen bonds with conserved residues on the sides and bottom of the peptide binding groove of class I molecules. These interactions are important for holding the peptides in the binding groove and for stabilizing the complex (Guo *et al* at page 366, column 1 lines 1-10.) "...the preferred length (of the peptide) is determined by the minimum amount of peptide required to span the center of the binding site and optimize the interactions at the ends" , but that the predominant length is 9 amino acid residues (Engelhard at page 14, column 1, lines 23-27). The minimum length for a peptide to be a T cell epitope for class II MHC is about 12 amino acid residues (Rammensee *et al* at page 181, column 2, first full paragraph).

In addition, the art recognizes that flanking sequences influence the processing and presentation of CTL epitopes (Eisenlohr *et al*, Shastri *et al*, Bergmann *et al*, Wang *et al*, Perkins *et al*, Theoboald *et al*and Gileadi *et al*) and that immunodominance can be affected by the context of the epitope within the protein molecule and that junctional neoepitopes can be created (Perkins *et al*) or that immunodominant epitopes can be completely silenced by contiguous sequences (Wang *et al*).

The specification provides no disclosure that modified 5T4 antigens encoded in the vector(s) of the claimed invention are immunogenic, either as CTL, Th or B cell epitopes. *In vivo* studies disclosed in the instant specification utilize whole unaltered human or murine 5T4 as enunciated supra. Celis *et al* teach that in order to establish whether a peptide is immunogenic said peptide needs to be tested in assays that actually establish that a peptide is immunogenic. Further, although *experimental* ranking schemes are available for predicting relative binding strengths of some HLA binding nonapeptides, and assays are available to test the binding of peptides to HLA, an undue amount of experimentation would be involved in determining peptides from the many possibilities that would be capable of binding to HLA, inducing a CTL response and producing a clinical endpoint. Celis *et al* teach that "In addition to MHC binding, other factors such as antigen processing, peptide transport and the composition of the T-cell receptor repertoire could determine whether peptides can function as effective CTL antigens." Ochoa-Garay *et al* teach that "In summary, the results in this report indicate that the immunogenicity of a peptide cannot always be predicted from its affinity for class I or the presence of class I binding motifs. In addition, our data show that variables such as CTL precursor frequency, peptide hydrophobicity and stability can influence the *in vitro* induction of CTL responses" (especially page 279, last sentence and continuing onto page 280). Karin *et al* teach that amino acids in an MHC binding peptide that are not the amino acids which participate in MHC binding can have a profound effect on whether or not a peptide is immunogenic. Chaux *et al* (Int. J. Cancer 77 538-542, 1998) teach that it is unclear if peptides from tumor specific proteins possessing anchor residues for binding to class I MHC produce CTL responses in patients vaccinated with the said peptides.

It would require undue experimentation to determine which of the trillions of modified 5T4 antigens encompassed by the claimed invention are immunogenic and which are not.

In addition, the specification provides no disclosure that the SEQ ID NO recited in instant claim 41 that were selected by prediction algorithm and shown to bind to HLA-A*0201 are immunogenic, *i.e.,* induce CTL, and can produce a clinical endpoint in inducing an anti-tumor immunotherapeutic response. Although the instant specification discloses that immunization with vector(s) encoding full-length unmodified human or murine 5T4 protein in mouse tumor models could produce a clinical response *in vivo*, there is no disclosure that the isolated SEQ ID NO can produce the clinical result, even if capable of inducing CTL.

Evidentiary reference Berger *et al* (Int. J. Cancer. 111: 229-237, 2004) teach "Since strong CTL responses as observed in this patient are the goal of cancer vaccination but are so far only rarely observed, the thorough analysis of patients exhibiting either exceptional clinical and/or immunologic response appears critical to understanding how vaccine therapies work and can be further improved." (abstract). Berger *et al* further teach "immune therapy for tumor patients aims at harnessing the immune system to fight cancer. Indeed, clinical trials have already shown that tumor-specific T cells can be induced even in advanced cancer patients. The induction of tumor-specific T cells, however, is not necessarily associated with a clinical response. A major obstacle in evaluating the success of a cell-based immunotherapy lies in the fact that systemic immune responses detected in the blood may not reflect the actual situation in the tumor." (column 1, page 229). Berger *et al* teach "...tumor-reactive T-cell clones persisted for prolonged time in circulation but failed to infiltrate the analyzed tumor lesions. A possible explanation for this discrepancy is provided by the recent report from a transgenic mouse model that tumors may develop an intrinisic resistance to leukocyte infiltration and effector function that prevents even persistently high levels of activated tumor-specific T lymphocytes from eradicating the tumor" (paragraph spanning columns 1-2 on page 236).

Evidentiary reference Celis (J. Clin. Invest. 2002, 110 (12: 1765-1768) teaches that "Unfortunately, the advantages that peptide vaccines have to offer are to some extent diminished by their inherent lack of immunogenicity, which so far has been reflected by their not-so-spectacular results in the clinic. Because the immune system in most species has evolved through time to fight life threatening infectious agents (and perhaps tumors), it should not be surprising that vaccines consisting of aseptic, endotoxin-free peptides are likely to be ignored and will likely be ineffective at inducing T cell immunity. In addition, peptides that are injected in aqueous solutions will be unsuccessful at stimulating CTL responses, either because of their rapid biodegradation (e.g., by proteases) or, worse, because of the induction of T cell tolerance/anergy, which results from the antigenic stimulation of CTLs by non-professional APCs." Celis further teaches that an additional complication resulting from the use of synthetic peptide-derived vaccines is the induction of low affinity CTLs, that while capable of killing target cells that are exogenously pulsed with peptide, are not able to recognize the target cells that naturally process and present the peptide epitope, such as malignant cells. These low quality CTLs would have little effect in fighting and controlling disease (especially page 1765 through the paragraph spanning pages 1765-1766.

Evidentiary reference Marchand *et al* (Int. J. Cancer 80: 219-230, 1999) teach "Considerable further progress is needed... before immunization with tumor-specific antigens recognized by T cells becomes an effective and generally applicable cancer therapy." (second to last sentence of article).

Evidentiary reference Marchand *et al* (Exp. Opin. Biol. Ther. 1(3): 497-510, 2001) teach "It is fair to say that in patients vaccinated with defined antigen, the immune responses induced have been so far very poor, if present. In some studies, immune responses were reported for some patients but without any correlation with the clinical responses. In addition, some patients with complete and long-term regressions of several melanoma metastases failed to mount a detectable response against the antigen present in the vaccine." (last paragraph at column 2 on page 505).

Evidentiary reference Bodey *et al* (Anticancer Research 20: 2665-2676, 2000) teach "while cancer vaccine trials have yielded tantalizing results, active immunotherapy has not yet become an established modality of anticancer therapy (page 2665 at column 2). Bodey *et al* further teach "the use of active specific immunotherapy for cancer is still in its infancy despite several decades of clinical and basic research" (page 2668 at column 2).

Evidentiary reference Gao *et al* (J. Immunother. 23: 643-653, 2000) found that although anti-tumor CTL response was enhanced by immunization, the tumors failed to regress due to an association with lack of CTL migration to the tumor sites (abstract). Thus, Gao *et al* teach that activation of peptide epitope-specific CTL is not an appropriate endopoint, and an estimation of efficacy based upon this factor is not predictive of actual efficacy of treatment *in vivo*.

Evidentiary reference Morel *et al* (Immunity 12: 107-117, 2000) teach the treatment of target cells for at least one week with IFN-γ to induce immunoproteasome expression in said target cells, and further teach that a number of antigenic peptides that are efficiently produced by the standard proteasome are not produced by the immunoproteasome. Morel *et al* further teach that a major difference between the two forms of proteasomes in terms of catalytic activity is the severely reduced ability of the immunoproteasome to cleave after acidic residues and also after residues with branched side chains, such as valine (paragraph spanning pages 113-114). Morel *et al* teach that an IFN-γ rich environment such as that found in a lymph node or a tumor mass heavily infiltrated with T cells could cause a proteasome switch in the tumor cells resulting in a lack of presentation of certain tumor antigens and escape from CTL attack (especially first sentence of the third full paragraph at column 1 on page 114).

Evidentiary reference Boon *et al* (Ann. Rev. Immunol. 2006, 24: 175-208) teach "Therapeutic vaccination of metastatic melanoma patients with these antigens [*i.e.*, melanoma antigens] is followed by tumor regressions in only a small minority of the patients (page 175, abstract). Boon *et al* further teach "In conclusion, therapeutic success following vaccination may not depend on the number of T cells produced directly by the vaccine, but rather on the production of a T cell clone with functional properties that enable it to migrate to the tumor and resist the local immunosuppressive environment long enough to initiate a regression process...To achieve therapeutic success, investigators will probably need to understand the cause of the local

immunosuppression in the tumors and find counteracting agents. As stated above, the list of possible immunosuppressive agents present in tumors is considerable. But it will be important to find whether, for each type of tumor, there is a prevalent immunosuppressive agent. Just as many types of tumors have preferred oncogenic pathways that differ from one type of tumor to another, each type of tumor may also have preferred immunosuppressive processes that we must identify to achieve therapeutic success...Therapeutic vaccination of cancer has not yet proved to be effective enough to become a generally applied cancer treatment...We do not believe that melanoma patients suffer from a degree of general immunosuppression, which we believe is restricted to very late-stage patients who are not included in most studies...Therefore, the difference in the quality of the response would be due to a chance event determining, for instance, the functional properties of the unique or the few responder T cell clones elicited by the vaccine. In that case, it will be essential to understand what this crucial functional property is. At the other extreme, the antivaccine T cell responses would be similar in all patients, but the level of resistance of the tumors would vary considerably. In that case investigators would need to identify the main component of this resistance and find ways to counteract it." (especially pages 193-194).

Accordingly, there is a high level of unpredictability in designing/selecting longer sequences or modified sequences that would be processed, still maintain binding function, elicit a CTL, Th or antibody response, and produce a clinical endpoint in inducing an anti-tumor immunotherapeutic response in a subject.

There is insufficient guidance in the specification as to how to make and/or use instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

Applicant's arguments have been fully considered, but are not persuasive.

Applicant's arguments are of record in the amendment filed 2/20/07 on pages 9-11, briefly that: (1) no prima facie case of non-enablement has been presented, (2) the instant rejection fails to provide evidence of undue experimentation, (3) no objective reasons why undue experimentation is necessary to make and use the claimed invention have been presented in terms of making vectors, modifying human 5T4 antigen sequences, or screening for modified antigens as containing an HLA CTL peptide epitope and/or capable of inducing an antitumor response in a subject.

It is the Examiner's position that the instant rejection does establish undue experimentation and makes a prima facie case of non-enablement. It is the Examiner's position that the instant rejection speaks to the breadth of the claims, the state of the art, the level of predictability in the art and to undue experimentation. Although one may predict which subsequences of an antigenic protein may bind to an individual HLA molecule and potentially function as a CTL epitope, the instant rejection enunciates that many factors contribute to immunogenicity, including the presence of flanking amino acid sequences, that the instant claims are drawn to a vector comprising a nucleotide sequence that encodes a peptide or a polypeptide of any length and composition as long as it contains an HLA CTL epitope of a 5T4 antigen. The evidentiary references establish that even if a CTL response is induced, it may not be sufficient for inducing an antitumor immunotherapeutic response in a subject. Thus, the instant rejection enunciates the unpredictability in designing or selecting sequences that would be processed, still maintain binding function, elicit a CTL, Th or antibody response, and produce a clinical endpoint in inducing an anti-tumor immunotherapeutic response in a subject.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 37, 39, 41, 48-51 and 53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 37 is indefinite in the recitation of "encoding human 5T4 antigen, wherein said human 5T4 antigen is modified to differ from a naturally occurring 5T4 antigen" because it is not clear what is meant, *i.e.,* how the human 5T4 antigen can be human 5T4 antigen if it is modified. The instant specification discloses that human 5T4 antigen is SEQ ID NO: 1.

b. Claim 53 is indefinite in the recitation of "human 5T4 antigen encoded by second vector is modified to differ from a naturally occurring 5T4 antigen" because it is not clear what is meant, *i.e.,* how the human 5T4 antigen can be human 5T4 antigen if it is modified. The instant specification discloses that human 5T4 antigen is SEQ ID NO: 1.

11. No claim is allowed.

12. The reference "AB" crossed out in Applicant's Form 1449 filed 3/14/07 is a duplicate entry of that listed on Applicant's Form 1449 filed 2/20/07. The reference "BF" crossed out in Applicant's Form 1449 filed 3/14/07 was not considered by the Examiner because the entire reference was not provided by Applicant.

13. The Examiner has considered references provided by Applicant on 2/22/07 that are listed on Applicant's Form 1449 filed 5/13/04 (a copy provided herewith to Applicant with notation of said references considered). Applicant is reminded that the Examiner has not considered other references crossed out on Applicant's Form 1449 filed 5/13/04, a copy of which was mailed to Applicant on 10/12/06.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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